

gatus) and prairie dogs (*Cynomys gunnisoni*) in Catron County.¹

Report of this first New Mexico plague case, with the attendant publicity, probably facilitated recognition of two subsequent but unrelated plague cases in New Mexico in 1949. From 1949 through 1982, a total of 114 cases with 22 fatalities were reported from New Mexico. Recognizing a rare disease is always a difficult accomplishment; consideration of plague in New Mexico and in other western states remains a challenge.^{5,6}

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Newer Forms of Insulin

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THE PURITY of insulin has changed dramatically in the past ten years and indications for the use of the newer and more purified forms are being established. There are now 42 insulin products in the United States, and at least six more products for human use will probably be approved soon by the Food and Drug Administration (FDA).

The term "purified insulin" is somewhat misleading because as each new purification step was adopted for use in commercial preparation of insulins, the product was described as "purified." Current FDA terminology, however, allows only insulins containing less than 10 ppm of proinsulin and other related residues to be called purified insulin. These insulins became available in the United States in 1980 and were an improvement over the conventional insulins, which contained up to 30,000 ppm of impurities.

The purified insulins are made from either beef or pork insulin, as are the standard insulins, though many of the standard insulins are combinations of both. Immunogenically, pork is preferable as an insulin source because only 1 of the 51 amino acids making up the insulin molecule is different from that in the human insulin molecule, compared with three different amino acids of the beef insulin molecule. The species differ enough immunologically to cause greater antibody formation in those persons exposed to purified beef insulin than in those treated with purified pork insulin.

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In the United States insulins now range in purity from 50 ppm to less than 10 ppm, with the purified insulins available only in concentrations of U 500 (500 units per ml) (for insulin-resistant states) and U 100. Other insulins can be obtained in U 40 concentrations, and insulin diluents are available for mixing concentrations that may be desired for use in insulin pumps or for making small doses such as for infants.

The indications for use of purified insulins are as follows:

- *Lipoatrophy* (pitting at the insulin injection site). This complication disappears when a patient is switched to purified pork insulin. Administration of purified insulin must be continued after resolution of the lipoatrophy, however, because reexposure to the less pure insulin, even though at a different injection site, can cause a reappearance of the atrophy that is resistant to subsequent treatment with the more purified forms. An immune component of lipoatrophy is suggested by the high coincidence of local allergy and lipoatrophy (15 percent) and the reduction of the atrophy with local injection of steroids.¹

- *Insulin hypertrophy* (fat hypertrophy at injection site). This complication may also have an immune component. It does not respond as predictably to therapy with purified insulins, however, with improvement occurring in only about half of the patients.²

- *Allergic reactions to insulin*. Allergic reactions take several forms. Local allergic responses to insulin are varied and can occur within 15 minutes to 2 hours after the injection or they can be delayed and not appear for 4 hours or more after the injection. Common allergies often occur one to four weeks after institution of insulin therapy or within a few days of reinstitution of insulin and are characterized by a hard, red induration at the injection site. The longer acting insulins are more likely to induce this response. Protamine, the agent that slows the action of isophane insulin suspension (NPH insulin), is itself a significant antigen. Systemic allergic responses can also occur and are characterized by urticaria or angioedema, or both, which is mediated by IgE antibodies. More than 60 percent of persons having systemic allergic reactions to insulin have had intermittent insulin therapy and 37 percent are allergic to penicillin. Systemic allergic reactions to insulin are potentially life threatening. If continuing insulin therapy is necessary, a patient should be desensitized in hospital using purified insulins according to the protocol accompanying the desensitization kit, and then maintenance doses of insulin must be administered to maintain the desensitization.

- *Antibody-mediated resistance to insulin*. Such resistance occurs equally in both sexes and usually appears within five years of institution of therapy (in 66 percent of these, insulin resistance develops within the first year). Onset is usually gradual and 75 percent of insulin-resistant patients are older than 40 years of age. About half of these patients need more than 1,000 units of insulin a day and occasionally more than 25,000 units a day is needed during a resistant phase.

Insulin resistance is usually self-limited and spontaneously resolves in six months to a year.³ Treatment with systemic steroids usually leads to abatement of insulin resistance in a few days but often releases previously antibody-bound insulin and therefore may precipitate hypoglycemia. Use of purified insulins in diabetic patients is expected to decrease the incidence of antibody-mediated insulin resistance.

- *A newly diagnosed case of diabetes.* Development of insulin antibodies is influenced by several factors, among which are species specificity (beef is more antigenic than pork), the physical state of the insulin preparation (modified insulins are more antigenic than regular or fast-acting insulins) and purity. The differences in chemical structures among porcine, bovine and human proinsulin are much greater than the differences among their insulin molecules; thus, contamination with proinsulin may lead to development of cross-reacting antibodies that bind to insulins. In newly diagnosed diabetic patients who have been treated with purified pork insulin for one to two years, insulin antibodies developed in only 10 percent, compared with 75 percent of patients treated with conventional pork insulin for one to two years.⁴ For this reason many diabetologists believe that all patients being started on insulin therapy for the first time should be treated with purified insulins. Other evidence⁵ suggests that more C-peptide (and insulin) secretory capacity may be preserved in new patients treated with purified insulin compared with those treated with conventional insulins.

- *Pregnancy is present or contemplated.* Conventional insulin treatment before pregnancy influences insulin antibody levels that will be present during pregnancy. Insulin antibodies freely pass to the fetus and may be related to neonatal morbidity. Switching to purified pork insulin during pregnancy produces significant falls in insulin antibody levels.⁶

- *Short-term or intermittent insulin therapy.* Patients in whom short-term or intermittent insulin therapy is

anticipated (that is, gestational diabetic women or acutely stressed type II diabetic persons) should be treated with purified insulin to minimize antibody formation and possible development of insulin allergy or insulin resistance.

Although it seems unlikely that the development of complications of diabetes would be affected by the purity of the insulin per se, the purity may affect development of complications indirectly by affecting the degree of control of diabetes. Insulin that is bound by antibodies is not immediately available to the cells and may lead to a later peak action of insulin preparations and a longer duration of insulin action. Thus, adjustments made to quickly correct hyperglycemia by using fast-acting insulins may not be so successful when large amounts of antibody are present.

Finally, although it would be desirable for all patients treated with insulin to be receiving purified preparations, the added expense is significant. Purification is the most costly step in insulin production, and for this reason biosynthetic human insulin produced using recombinant DNA technology or chemical modification of pork insulin cannot be expected to lessen the cost. Purified insulins cost about \$4.50 to \$7 more per vial than conventional insulins in community pharmacies. Many patients are unwilling or unable to bear this added expense.

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